REMARKS

The foregoing amendments to the claims are of a formal nature and do not add new matter. Claims 1-6 stand rejected for allegedly being unpatentable under 35 U.S.C. §§101 and 112, first paragraph, and under 35 U.S.C. §102. For the reasons set forth below, Applicants respectfully traverse.

Claim 6 has been cancelled and Claim 1 amended; thus, Claims 1-5 are present for examination. The changes made to the Specification and Claims by the current amendment, including ~~deletions~~ and additions, are shown herein with deletions designated with a strikethrough and additions underlined.

Specification

The title of the invention has been amended to better describe the claimed invention. In addition, embedded hyperlinks have been removed.

The PTO has stated that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). The PTO states that the application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 because the application does not contain, as a separate part of the disclosure on a paper copy, a "Sequence Listing" as required by 37 C.F.R. § 1.821(c).

Applicants submit herewith a response to the Notice to Comply which amends the specification to include a paper copy of the "Sequence Listing," which is also submitted herewith.

Correction of Inventorship under 37 CFR §1.48(b)

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

IDS

Applicants submit herewith an IDS separately listing references recited in the BLAST report in order to be compliant with 37 C.F.R.§1.98(a)(1). Consideration of this Information Disclosure Statement is respectfully requested.

Priority

As discussed in detail below, Applicants rely on the gene expression data for patentable utility. This data was first disclosed in PCT/US00/23328, filed August 24, 2000, on page 93, line 3. Priority to this application has been properly claimed in the present application. Hence, the present application is entitled to at least the priority date of **August 24, 2000**.

Rejection under 35 U.S.C. §101 and §112

The Examiner rejected Claims 1-6 as lacking specific utility under 35 U.S.C. § 101 allegedly because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility under 35 U.S.C. § 101. Claims 1-6 are also rejected under 35 U.S.C. § 112, first paragraph for lack of utility. According to the Examiner, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. Applicants respectfully disagree with and traverse these rejections.

The Examiner asserts that since the protein recited in the claims, PRO1013 (SEQ ID NO:22), is not supported by a specific and substantial asserted utility or well-established utility, the antibodies to this polypeptide also lack utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." A utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any*

reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guideline restate the Patent Office's long-established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record ... that is probative of the Applicant's assertions." (M.P.E.P. 2107 II(B)(1)(ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Absolute predictability is not a requirement. Only after the Examiner has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

The PTO argues that the invention lacks specific and substantial utility because there is no necessary correlation between a specific disease state and the expression of the PRO1013 polypeptide. The utility of the claimed antibody depends upon whether or not the polypeptide it binds has utility and enablement. According to the PTO, the invention lacks any "real world" context of use for PRO1013 proteins and antibodies.

The claims are directed to antibodies that bind to SEQ ID NO:22 (encoding PRO1013). The specification, in Example 18, discloses that the nucleic acid encoding PRO1013 (DNA56410-1414) is more highly expressed in normal stomach as compared to stomach tumor.

As an initial matter, Applicants rely on the gene expression data for patentable utility for this case, which was first disclosed in PCT/US00/23328, filed August 24, 2000. Applicants have properly claimed and are entitled to the priority of the effective filing date of **August 24, 2000**. As will be apparent from the discussions below and the supporting evidence, Applicants submit that the gene expression data provide specific and substantial asserted utility for the PRO1013 polypeptide and the claimed antibodies. Since this utility was disclosed in PCT/US00/23328 on page 93, line 3, through page 96, line 35, the claims pending are fully entitled to the priority of August 24, 2000.

The gene expression data in Example 18 was obtained using standard semi-quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a semi-quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type rendered the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor, as well as therapeutically, as a target for the treatment of a tumor in a subject possessing such a tumor. Applicants submit herewith the declaration of J. Christopher Grimaldi, an expert in the field of cancer biology as Exhibit A. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal tissue and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Contrary to the PTO's assertions that this makes the data unreliable, Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more

> generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO also argues that because cancerous tissue can be aneuploid, and the data in the instant application was not corrected for aneuploidy, "a higher amplification of a gene does not necessarily mean higher expression or lower in a tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action at 6. The PTO relies on a single reference, Sen, 2000, Curr. Opin. Oncol. 12:82-88 (hereinafter Sen).

Applicants agree that Sen teaches that most cancerous tissues are aneuploid, and that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells tested. However, Applicants fail to see how it is relevant to the utility of the claimed polypeptides, or their corresponding antibodies, whether the over and under-expression reported in Example 18 is due to aneuploidy or not. Regardless of whether the under-expression of the gene encoding PRO1013 is a result of decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is under-expressed in stomach tumor as

compared to normal tissue, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer.

Applicants have established that the accepted understanding in the art is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein

The PTO argues that there is no supporting evidence that the PRO1013 polypeptide is under-expressed in the tumor tissue compared to the normal tissue. The PTO also states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. Relying on Pennica *et al.*, 1998, PNAS USA 95:14717-14722 (hereinafter Pennica), the PTO states that one cannot extrapolate the expression data provided in the specification to support the implicit assertion that the PRO1013 polypeptides and antibodies can be used in cancer diagnosis or therapy.

Applicants respectfully submit that the PTO is confusing the relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased expression of a gene or mRNA expression on the other. The PTO focuses on the statement from Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 7. As an aside, it should be noted that this result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicates that there are more copies of the mRNA encoding PRO1013 in normal stomach than in stomach tumor. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants further submit that it is generally well-understood in the art that in the majority of cases, gene expression correlates with levels of protein expression. In support of Applicants' position, Applicants submit herewith as Exhibit B a second Declaration by J. Christopher Grimaldi. This declaration was originally submitted in connection with co-pending application Serial No. 10/006,867. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be overexpressed....This same principle applies to gene under-expression." The references cited in the declaration and submitted herewith support this statement.

Scientists regularly rely on the results of gene expression to point the way to differential protein expression in disease and, in this case, cancer. Submitted herewith as Exhibit C is the declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a

particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Additional references support this position. For example, Orntoft et al. (submitted herewith as Exhibit D) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft et al. showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman et al. (submitted herewith as Exhibit E) showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels" (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack et al. (submitted herewith as Exhibit F) who studied a series of primary human breast tumors and found that "...62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels" (see column 1, abstract). Thus, these articles collectively teach that in general, gene expression correspondingly influences mRNA expression.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of cases, the combined teachings in the art, exemplified by Orntoft et al., Hyman et al. and Pollack et al. and the Grimaldi and Polakis declarations, overwhelmingly teach that gene expression influences protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the gene expression data for the PRO1013 gene, that the PRO1013 protein is concomitantly

under-expressed in stomach tumor. Thus, Applicants submit that the PRO1013 protein and antibodies against it have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

Claimed antibodies would have diagnostic utility even if the protein were not over-expressed

Even assuming *arguendo* that, there is no correlation between gene expression and increased or decreased protein expression for PRO1013, which Applicants submit is not true, the polypeptide encoded by a gene that is under-expressed in cancer would still have a credible, specific and substantial utility. In support, Applicants submit herewith as Exhibit G the Declaration of Avi Ashkenazi, Ph.D., an expert in the field of cancer biology. Dr. Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

This is echoed by Mr. Grimaldi in paragraph 6 of his Declaration (Exhibit B) where he states that "even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment."

Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if the gene-product, the protein, is not over- or under-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's and Mr. Grimaldi's Declarations, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is over-expressed in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith as Exhibit H. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO 1013 polypeptide and antibodies against the PRO1013 polypeptide. Based on the evidence and arguments presented herein, one skilled in the art, at the time the application was filed, would know how to use the claimed antibodies.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Applicants have provided several expert opinions and references supporting the utility of the present invention. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made by Mr. Grimaldi, and Dr. Polakis and Dr. Ashkenazi, and must treat as true the statements made by these experts. Applicant reminds the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001).

Given the totality of the evidence provided, Applicants submit that they have established a specific and substantial credible utility for the claimed proteins as diagnostic agents. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the PRO1013 polypeptide set forth in the specification. In view of the above arguments, Applicants respectfully request that the PTO reconsider and withdraw the utility rejections under 35 U.S.C. §101 and §112, first paragraph.

35 U.S.C. §112, second paragraph

The Examiner rejected Claims 1-6 as indefinite for the recitation of "an antibody that binds" and an "antibody that specifically binds". Claim 6 has been cancelled and Claim 1 amended to recite "specifically binds". Applicants submit that the term "specifically binds" has a well established meaning and is understood by those skilled in the art to mean that the antibody binds to a particular polypeptide, and does not significantly bind to any other polypeptide. Since claim terms should be given their ordinary, art-recognized meaning, the present rejection is believed to be misplaced, and should be withdrawn.

Rejection under 35 U.S.C. §102(e)

The Examiner rejected Claims 1-6 as anticipated under 102(e) by Edwards et al (6,639,063, issued October 28, 2003, filed July 21, 2000). Because of the allegations of the lack of utility for the claimed invention, the Examiner has accorded an effective priority date for this application of its instant filing date. Consequently, the Examiner has cited this reference as prior art against the instant claims and have alleged that the claims are unpatentable in view of this reference. Applicants respectfully traverse.

Applicants can find no disclosure in the cited '063 patent of any utility whatsoever for the polypeptide of SEQ ID NO:3917, merely a disclosure of the sequence itself. Applicant's first disclosure of the sequence of the PRO1013 polypeptide (SEQ ID NO:22) was in Application No. 60/088,029 filed June 4, 1998. Applicants have properly claimed priority to this application, and are entitled to rely on this application's earlier filing date. Applicants have therefore shown possession of the claimed invention prior to the cited reference.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound

called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited reference. Applicants demonstrated, by means of the disclosure of SEQ ID NO:2 in their provisional application filed June 4, 1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID

NO:22, as disclosed in the Edwards reference dated July 21, 2000. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §102(e) be withdrawn.

Conclusion

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 19, 2004

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